

country and working as a gardener for one of the writers for about a month following the termination of the observations made in the hospital. He had improved markedly in strength, beginning with light work and increasing until he was able at the time mentioned to mow a rather large lawn without undue fatigue. On a diet containing oatmeal for breakfast, one slice of bread at each meal, and two glasses of milk, besides green vegetables and plenty of meat, his urine contained only 30.9 grams of glucose. This was the day before fasting. The fasting urine, begun at 7 A.M., twelve hours after his last meal, contained only the faintest possible trace of glucose, not more than is often found in normal urines.

The patient returned to the city October 1, 1916, and found work as a street-car conductor. His urine at this time contained a considerable amount of sugar, which was not quantitatively estimated.

---

## CLINICAL STUDIES OF ACIDOSIS.

BY J. HAROLD AUSTIN, M.D.,

AND

LEON JONAS, M.D.,

WOODWARD FELLOW IN PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF PENNSYLVANIA,  
PHILADELPHIA.

(From the William Pepper Laboratory of Clinical Medicine, University of  
Pennsylvania.)

DURING the past few years much progress has been made in the study of the regulation of the body fluids as regards acidity and alkalinity and in the development of our conception of the condition known as acidosis.

Acidosis may well be compared with disturbance of the body temperature. It is recognized that life can continue only within a limited range of temperature variation and that health is compatible only with a still more restricted range. We are, more or less, familiar with the mechanisms which regulate the body temperature and maintain its constancy. Similarly, we have learned that the reaction of the body fluids as regards acidity and alkalinity must possess a degree of constancy even greater than must their temperature, if a normal condition or, indeed, life itself is to continue. Largely through the work of Lawrence Henderson,<sup>1</sup> and

<sup>1</sup> Clinical Studies on Acid Base Equilibrium and the Nature of Acidosis, *Arch. Int. Med.*, 1913, xii, 153. Sellards, A. W., the Determination of Equilibrium in the Human Body between Acids and Bases, with Especial References to Acidosis and Nephropathies, *Bull. Johns Hopkins Hosp.*, 1912, xxiii, 289.

his associates we have become familiar with at least some of the mechanisms by which this reaction is kept constant. The normal reaction in the body is maintained chiefly by three means: The first of these is the presence in the blood and lymph of the salts, chiefly the sodium salts, of two very weak acids, carbon dioxide and phosphoric acid. Of these two acids the former is the more abundant and important. In the blood and lymph, sodium carbonate (alkaline) and carbon dioxide (acid) are both present in such proportion as to give a nearly neutral reaction. Similarly disodium hydrogen phosphate (alkaline) and monosodium phosphate (acid) are both present in the proportions to give the same nearly neutral reaction. If to this almost neutral fluid a stronger acid, such as oxybutyric or lactic or hydrochloric acid be added, there occurs an interchange which diagrammatically may be expressed as follows: Each unit of strong acid combines with sodium of the salts of these weak acids, thereby liberating one unit of weak acid for each unit of strong acid introduced.

Sodium phosphate + hydrochloric acid = sodium chloride + phosphoric acid.

Sodium carbonate + hydrochloric acid = sodium chloride + carbon dioxide.

Thus for every unit of strong acid introduced into the blood there is liberated a unit of weak acid which possesses much less power of altering the reaction of the blood. The capacity of a free acid in a given concentration to alter the reaction of a fluid is dependent upon its ionization. For example, in a decinormal solution of hydrochloric acid, 91 per cent. of the hydrogen is dissociated in aqueous solution at ordinary temperature. Thus:

$1000 \text{ HCl} = 910 \text{ H}^+ + 910 \text{ Cl}^- + 90 \text{ HCl}$ ; on the other hand, in a decinormal solution of acetic acid only 1.3 per cent. of the reacting hydrogen is dissociated under similar conditions. Thus:  $1000$

$\text{H}(\text{C}_2\text{H}_3\text{O}_2) = 13 \text{ H}^+ + 13 \text{ C}_2\text{H}_3\text{O}_2^- + 987 \text{ H}(\text{C}_2\text{H}_3\text{O}_2)$ . Hence, a decinormal solution of hydrochloric acid although containing the same amount of reacting hydrogen as a decinormal solution of acetic acid is seventy times as strong an acid as the acetic acid, because the hydrogen ion concentration of the hydrochloric acid is seventy times as great as that of the acetic acid. The reaction, the color of an indicator added to a solution and in general the properties which we group under the term acidity are dependent upon the hydrogen ion concentration of the solution.

For the purpose of denoting the hydrogen ion concentration or reaction of a solution the notation now generally used in medical work is the logarithmic notation. In this notation the hydrogen ion concentration of a neutral solution is about 7; increasing degrees of acidity are indicated by decreasing figures and increasing degrees of alkalinity by increasing figures. By this notation the reaction of

urine ranges, according to Henderson and Palmer,<sup>2</sup> depending upon the character of the diet and other factors between the acid urine 4.7 and the alkaline urine 8.7. As a rule, it lies between 5 and 7.5. The blood possesses a very constant reaction at 7.4.

The first factor, therefore, in maintaining the constancy of reaction of the blood is the presence of considerable amounts of sodium carbonate with carbon dioxid and of sodium phosphate in the blood. When acids are added to the blood they combine with this sodium and liberate carbonic and phosphoric acids, both having very low coefficients of dissociation, hence producing a minimal change in the hydrogen ion concentration of the blood. This factor alone is extremely potent in diminishing the changes in the reaction of the blood and body fluids when subjected to the addition of acids or alkalies. The second and third factors are the rapid elimination from the body of these weak acids when so liberated, the phosphoric acid being eliminated by the kidney and the carbonic acid by the lungs. To these weak salts constituted with the weak acids, the sodium phosphate and sodium carbonate, Henderson has given the name "buffer substances," because of their effect in limiting the changes in reaction that would follow the introduction of acids or alkalies into the blood. As a result of their presence in the body fluids and of the rapid elimination by the lungs and kidneys of the carbonic acid and phosphoric acid liberated from them the blood and body fluids always preserve that constancy of reaction essential to life. It must be clear, however, that the continued introduction of acids into the blood will tend to reduce the amount of these buffer substances available, and must invariably do so if their depletion exceeds the body's capacity for replacing them. When such a reduction in the buffer substances of the blood has occurred the condition is that known as "acidosis." Acidosis may be defined as any condition in which the buffer substances of the blood and body fluids are reduced below the normal. The primary effect of such a reduction is a diminution in the capacity of the blood to transport acids or alkalies. The acid most abundantly produced in the body is carbonic acid, and when there is a reduction of the buffer substances of the blood there is a reduction in the blood's capacity for carrying carbonic acid. If this be marked enough there occurs an accumulation of carbonic acid in the tissues, and among other tissues in the respiratory center. As is well known, any increase of the acidity in the respiratory center, such as will be induced by an accumulation of  $\text{CO}_2$ , serves as stimulant to this center. A more thorough ventilation of the lungs results. A more thorough ventilation of the blood follows, and this favoring the removal of the  $\text{CO}_2$  from the tissues, limits its further accumulation. Hence, an equilibrium

<sup>2</sup> Extreme Variations of the Concentration of Ionized Hydrogen in Human Urine, *Jour. Biol. Chem.*, 1913, xiv, 81.

is established as a result of the response of the respiratory center to the carbon dioxide stimulation, and there is maintained an increased respiratory activity with more thorough ventilation of the lungs. This adjustment gives us one clinical symptom of acidosis, namely, hyperpnea, and one of our laboratory methods for detecting acidosis, namely, the reduction in the carbon dioxide concentration of the alveolar air; the latter, of course, being used as a measure of the thoroughness of pulmonary ventilation. Since the carbon dioxide tension of the alveolar air is, at least under normal conditions of the lungs, equal to the carbon dioxide tension of the arterial blood leaving the lungs, this increased ventilation of the lungs with lowering of the carbon dioxide tension of the alveolar air leads also to a lowering of the carbon dioxide tension of the arterial blood. It is well to emphasize the distinction between carbon dioxide tension and carbon dioxide content of a fluid or atmosphere. Like any other gas, carbon dioxide, whether in the air or dissolved in fluid, is present at some definite pressure or tension. In air the relation between the percentage of carbon dioxide and its pressure or tension is a simple one. Its pressure bears the same proportion to the total pressure of the air that its volume does to the total volume of the air. Thus, if carbon dioxide constitutes 6 per cent. of a sample of air, and that air is at atmospheric pressure (barometric pressure), which at the time is, let us suppose, 765 mm. of Hg., then the carbon dioxide tension in the sample of air will be 6 per cent. of 765, or 45.9 mm. Hg. The carbon dioxide of the alveolar air may be expressed either in per cent. or in mm. of Hg. tension, usually the latter. The carbon dioxide tension of a fluid is the pressure which the carbon dioxide exerts at the surface of the fluid. It is measured by determining the carbon dioxide which must be maintained in an atmosphere in contact with the fluid in order to keep the carbon dioxide content of the fluid unchanged. If the carbon dioxide tension of the atmosphere contiguous to a fluid is greater than that of the fluid the fluid absorbs carbon dioxide until the tension in each is equal, and *vice versa*. The amount or percentage of carbon dioxide, however, which a fluid must contain to possess a certain carbon dioxide tension varies greatly, depending upon the nature and temperature of the fluid. This is illustrated in the following table, giving the approximate carbon dioxide content and carbon dioxide tension of distilled water, a sample of blood and of serum at 38°. If acid be added to any fluid the carbon dioxide content of the fluid will be decreased for any given carbon dioxide tension. Reduction of the temperature increases the carbon dioxide content for any given carbon dioxide tension.

It is, of course, the carbon dioxide tension, not content, of alveolar air and of arterial blood which are equal. In some of the discussions of this subject it has been stated that in acidosis the carbon dioxide tension of the blood is decreased. This statement is open to criticism. In acidosis the total carbon dioxide content of the

blood (carbonate plus free carbon dioxid) is decreased; the amount of  $\text{CO}_2$  that the blood can carry at a given  $\text{CO}_2$  tension is decreased. As a result of stimulation of the respiratory center the pulmonary ventilation is greater, hence the  $\text{CO}_2$  tension of the alveolar air and hence of the arterial blood is lower than normal; but, however much the total carbon dioxid content of the blood, arterial and venous, is reduced following the introduction of acids into the blood, and however much the carbon dioxid tension of the arterial blood is decreased by the increased respiratory activity, there is no proof that the carbon dioxid tension of the venous blood is decreased; indeed, it is possible that it may even be increased. Adequate studies upon this point are difficult, and are not yet available. Until the last few months only the very indirect method of gauging the existence of acidosis, namely, the determination of the thoroughness of pulmonary ventilation by estimating the carbon dioxid content or tension of the alveolar air, was our best laboratory method for the recognition of acidosis. The technic of this method has been greatly simplified recently by Marriott,<sup>3</sup> so that it may be carried out at the bedside in about five minutes' time and without any complicated apparatus. The value of this method has always been limited, however, first, by the fact that as a gauge of the state of the blood it is dependent upon a normal irritability of the respiratory center. A hyperirritability of the respiratory center will maintain an increased pulmonary ventilation and a lowered alveolar  $\text{CO}_2$  content without there being any acidosis, and conversely a diminished irritability of the respiratory center may diminish the evidence by this method of an existing acidosis. In the second place an alteration in the pulmonary ventilation may readily occur from unintentional alteration by the patient of his manner or rate of breathing during the time of examination. Moreover, in certain conditions, such as Cheyne-Stokes breathing, the pulmonary ventilation is variable and in pulmonary disease, such as pneumonia, we do not yet know what effect the local disease has upon the relation between the pulmonary ventilation and the state of the blood.

AMOUNT OF  $\text{CO}_2$  IN VOLUMES PER CENT. HELD IN DISTILLED WATER, IN A SAMPLE OF WHOLE BLOOD (BOHR) AND IN A SAMPLE OF SERUM (JACQUET) AT THE SAME TEMPERATURE,  $38^\circ$ , AND THE INDICATED  $\text{CO}_2$  TENSIONS.

| $\text{CO}_2$ tension in mm. Hg. | Volumes per cent. of $\text{CO}_2$ in |                           |                     |
|----------------------------------|---------------------------------------|---------------------------|---------------------|
|                                  | Water,<br>per cent.                   | Whole blood,<br>per cent. | Serum,<br>per cent. |
| 15 mm. . . . .                   | 1.1                                   | 30.5                      | 47.2                |
| 30 mm. . . . .                   | 2.2                                   | 38.9                      | 62.1                |
| 50 mm. . . . .                   | 3.7                                   | 45.3                      | 64.6                |

Fortunately, for the progress of our knowledge of acidosis, two methods have been given us during the past year which enable

<sup>3</sup> The Determination of Alveolar Carbon Dioxid Tension by a Simple Method, Jour. Am. Med. Assn., 1916, lxxvi, 1594.

us to study directly from the blood itself the "buffer value" of the blood. The first devised by Van Slyke, Stillman, and Cullen<sup>4</sup> is a method for measuring directly by means of a special gas buret the amount of the sodium carbonate buffer in the blood. The second, devised by Levy, Rowntree, and Marriott,<sup>5</sup> is a method for gauging the same factor indirectly by determining the hydrogen ion concentration of a sample of the blood under certain conditions.

The first of these methods has been used by us in a series of clinical cases, and the results of these studies are here presented, together with some considerations concerning certain features of the technic.

The principle of this method is to obtain blood from the patient, oxalate it, separate the plasma and subject the latter to an atmosphere of definite carbon dioxid content or tension, about 6 per cent. (45 mm. tension). When the plasma has been brought into equilibrium with this atmosphere 1 c.c. of the plasma is transferred to a special gas buret, and by means of acid and a vacuum all the CO<sub>2</sub> held as carbonate is liberated and the total CO<sub>2</sub> drawn from the plasma into the vacuum and measured. The total CO<sub>2</sub> content after reduction to 0°, 760 mm. pressure, and correction for vapor tension, may be expressed as volumes per cent. of the original plasma. Thus, 1 c.c. of normal human plasma so treated will yield about 0.70 c.c. of CO<sub>2</sub>, or seventy volumes per cent.

TECHNIC. Upon first using this method we employed oxalated plasma obtained in the usual way by centrifuging the oxalated blood in open centrifuge tubes. The results secured were frequently surprising, however, and especially the remarkable variations often observed in repeated examinations of the blood of the same individual at different times. Investigation of the various steps in our procedure showed that these irregularities were due to the fact that the carbon dioxid binding capacity of a plasma is greatly influenced by the carbon dioxid tension present in the whole blood at the moment the cells and plasma are separated. If the carbon dioxid tension of the whole blood be high at the time of the separation into cells and plasma the plasma will have a higher binding capacity for carbon dioxid at any given tension than if the carbon dioxid tension of the whole blood be low at the time of the separation. This relation first pointed out by Zuntz<sup>6</sup> has been subsequently more thoroughly investigated by Guerber<sup>7</sup> and Petry.<sup>8</sup>

<sup>4</sup> Nature and Detection of Diabetic Acidosis, *Proc. Soc. Exper. Biol. and Med.*, 1915, xii, p. 165.

<sup>5</sup> A Simple Method for Determining Variations in the Hydrogen ion Concentration of the Blood, *Arch. Int. Med.*, 1915, xvi, 389.

<sup>6</sup> Bohr, C., Blutgase und respiratorischer Gaswechsel. In Nagel, W.: *Handb. der Physiol. des Menschen*, 1905, i, 116. Zuntz: *Beiträge zur Physiologie des Blutes*, Inaug. Diss., Bonn, 1868.

<sup>7</sup> Ueber den Einfluss der Kohlensäure auf die Verteilung von Basen und Säuren zwischen Serum und Blutkörperchen, *Sitzbericht. d. phys. med. Gesellschaft z. Würzburg*, 1895-96, p. 28.

<sup>8</sup> Ueber die Verteilung der Kohlensäure im Blute, *Beiträge z. chem. Phys. und Path.*, Hofmeister, 1902-3, iii, 247.

By these observers it was shown that when  $\text{CO}_2$  escapes from the plasma of whole blood and leaves behind the base chiefly sodium, with which it has been combined, thus increasing the alkalinity of the plasma, a diffusion of hydrochloric acid occurs from the cells into the plasma to combine with at least a part of this free base. If this plasma is now separated from the cells its combining power for  $\text{CO}_2$  is obviously less than that of the original plasma, since a portion of its base originally capable of holding  $\text{CO}_2$  is now combined with hydrochloric acid diffused from the cells. When the whole oxalated blood is drawn and centrifuged in the ordinary way in open tubes a variable escape of  $\text{CO}_2$  occurs during the process, and consequently from the same portion of blood, plasmas of very different binding capacities may be secured. It is in our experience highly important that either the escape of  $\text{CO}_2$  from the blood be prevented from the time the blood is drawn until the removal of the plasma from the cells, or else that the blood be brought to some standard carbon dioxide tension at the time of centrifuging and kept at this tension until the plasma is separated. We are indebted to Dr. Van Slyke<sup>9</sup> for the suggestion of a simple method for securing the former of these two conditions. This consists of drawing the blood directly from the patient's vein through tubing which passes to the bottom of a centrifuge tube containing a few oxalate crystals and which ends beneath a layer of paraffin oil. The oil floating above the blood effectually prevents the escape of  $\text{CO}_2$  until the centrifuging is complete and the plasma pipetted off. This paraffin oil method has been our standard method in these studies. In some cases, however, we have also saturated the whole oxalated blood at a tension of 6 per cent.  $\text{CO}_2$  and kept it at this tension by stoppering or by covering with paraffin oil during the centrifuging.

To show the importance of this step we obtained in a series of seventeen cases the oxalated plasma from the whole blood in three ways: (1) blood drawn from the vein directly into a centrifuge tube beneath paraffin oil and hence protected from loss of  $\text{CO}_2$  until removal of the plasma; (2) blood drawn and oxalated, exposed to the air, but subsequently saturated at 6 per cent.  $\text{CO}_2$  tension and kept at this tension during centrifuging; (3) blood drawn, oxalated, and centrifuged in the ordinary way exposed throughout to the air. The plasmas obtained in these three ways were all saturated at 6 per cent.  $\text{CO}_2$  tension and analyzed for their  $\text{CO}_2$  content by Van Slyke's method. The results are shown in Table I, A. It will be seen that the paraffin oil and the 6 per cent. saturation of the whole blood give closely parallel results, the latter, as a rule, yielding a plasma that holds from 3 to 6 more volumes per cent. of  $\text{CO}_2$ . On the other hand the exposed blood

<sup>9</sup> Personal communication.

invariably yields a plasma of lower binding capacity, but in different individuals or in the same individual at different times the resulting plasma may be only one volume per cent. lower, or as much as 24 volumes per cent. lower.

TABLE I.—PART A.—THE EFFECT OF THE CO<sub>2</sub> TENSION OF THE WHOLE BLOOD UPON THE CO<sub>2</sub> CAPACITY OF THE PLASMA DERIVED FROM IT.

| Case No. | CO <sub>2</sub> content of plasma saturated at 45 mm. CO <sub>2</sub> tension, the whole blood having been |   |      |                 |      |
|----------|--|---|------|-----------------|------|
|          | Kept under paraffin oil.   | Saturated at 45 mm. CO <sub>2</sub> at 20° C. | S-P. | Exposed to air. | P-E. |
|          | P.   | S.  |      | E.              |      |
| 1        | 73   | 77  | 4    | 50              | 23   |
| 2        | 73   | 72  | -1   | 51              | 22   |
| 3 }      | 70   | 66  | -4   | 68              | 2    |
| 3 }      | 66   | 68  | 2    | 49              | 17   |
| 4 }      | 66   | 70  | 4    | 49              | 17   |
| 5        | 65   | 68  | 3    | 49              | 16   |
| 6        | 64   | 73  | 9    | 48              | 16   |
| 7        | 64   | 68  | 4    | 57              | 7    |
| 8 }      | 64   | 68  | 4    | 43              | 21   |
| 8 }      | 62   | 68  | 6    | 50              | 12   |
| 9        | 62   | 68  | 6    | 59              | 3    |
| 10       | 60   | 64  | 4    | 55              | 5    |
| 11       | 59   | 62  | 3    | 38              | 21   |
| 12       | 53   | 59  | 6    | 43              | 10   |
| 13       | 52   | 58  | 6    | 44              | 8    |
| 14 }     | 51   | 49  | -2   | 38              | 13   |
| 14 }     | 46   | 48  | 2    | 45              | 1    |

If the oxalated blood before centrifuging be thoroughly aerated by being poured from beaker to beaker for five minutes the resulting plasma exhibits a still lower CO<sub>2</sub> capacity, as shown in Table I, B.

#### PART B.

| Case No. | Kept under paraffin oil. | Aerated 5 minutes | P-A. |
|----------|--------------------------|-------------------|------|
|          | P.                       | A.                |      |
| 15       | 70                       | 48                | 22   |
| 16       | 70                       | 59                | 11   |
| 17       | 66                       | 47                | 19   |
| 18       | 65                       | 46                | 19   |
| 19       | 64                       | 49                | 15   |
| 20       | 61                       | 44                | 17   |
| 21       | 58                       | 51                | 7    |

At first sight it might seem surprising that saturation of the whole blood at 6 per cent. (45 mm.) CO<sub>2</sub> tension should increase the CO<sub>2</sub> capacity of the plasma as compared with the blood as drawn from the vein under paraffin oil. That this occurs is due to the fact that the saturation of the whole blood at 45 mm. tension was carried out at room temperature (18° to 20° C.), and the blood will, as a rule, hold more CO<sub>2</sub> at 18° C. at 45 mm. tension than at the same or higher tension that exists in the veins at 37° C.

EFFECTS OF CYANOSIS. In considering the relative merits of the paraffin oil method and the 6 per cent. saturation of the whole



blood in the study of acidosis it will be recognized that most factors will alter the plasma in the same direction and about equally whichever of these methods be used. One conspicuous exception to this relation exists, however, namely, any alteration in the  $\text{CO}_2$  tension of the venous blood as drawn, such, for example, as occurs in asphyxia or cyanosis. This may be seen in the experiments shown in Table II.

TABLE II.—EFFECT OF INJECTION OF ACID, ALKALI, AND OF ASPHYXIA ON THE  $\text{CO}_2$  CAPACITY OF THE PLASMA.

| Dog No. | Blood drawn after:                 | CO <sub>2</sub> content of plasma saturated at 45 mm. CO <sub>2</sub> tension, the whole blood having been |   |       |
|---------|------------------------------------|--|---|-------|
|         |                                    | Kept under paraffin oil.   | Saturated at 45 mm. CO <sub>2</sub> at 20° C. | S- P. |
| 1       | Control period . . .               | P. 54  | S. 56   | 2     |
|         | $\text{KH}_2\text{PO}_4$ . . . . . | 47   | 52  | 5     |
|         | Asphyxia . . . . .                 | 48   | 46  | -2    |
|         | $\text{Na}_2\text{CO}_3$ . . . . . | 67   | 70  |       |
| 2       | Control period . . .               | 52   | 62  | 10    |
|         | Asphyxia . . . . .                 | 55   | 58  | 3     |
|         | $\text{KH}_2\text{PO}_4$ . . . . . | 48   | 58  | 10    |

These experiments were performed to show the effect upon the  $\text{CO}_2$  binding capacity of the plasma of injection of alkalis, of injection of acids, and of increase in the  $\text{CO}_2$  tension of the venous blood from asphyxia.

EXPERIMENT I. A normal dog, weighing 10 kilos, was etherized; 10 c.c. of blood drawn and oxalated under paraffin oil from the right jugular vein and immediately a second portion of 10 c.c. drawn and oxalated exposed to the air for subsequent saturation as whole blood at 6 per cent.  $\text{CO}_2$  (control blood). There was then injected in the course of fifteen minutes 150 c.c. of  $\text{KH}_2\text{PO}_4$  solution (13.6 gms. per liter) into the left femoral vein. Two portions of blood were immediately taken from the right jugular vein as before ( $\text{KH}_2\text{PO}_4$  blood). The trachea was then compressed until the tongue was deeply cyanosed and two more portions of blood taken as before from the right jugular vein (asphyxia blood). After a few minutes' interval 150 c.c. of 3 per cent.  $\text{Na}_2\text{CO}_3$  solution was injected in fifteen minutes into the left femoral vein and two portions of blood taken as before from the right jugular vein ( $\text{Na}_2\text{CO}_3$  blood). The injection of acid phosphate reduced the  $\text{CO}_2$  capacity of the plasma obtained both by the paraffin oil and by the 6 per cent. saturation method. Asphyxia still further reduced the  $\text{CO}_2$  capacity of the plasma by the 6 per cent. saturation method, but slightly increased that of the plasma from the paraffin oil method. Thus a slight acidosis of asphyxia was wholly obscured by the increased  $\text{CO}_2$  tension of the venous blood when the plasma was obtained by the paraffin oil method.

EXPERIMENT II. This experiment is identical, except that the asphyxia was performed before the injection of the acid phosphate.

The results are similar, but perhaps even more striking. Whether this effect of asphyxia upon the plasma obtained by the paraffin oil method would ever be of clinical importance is not certain, but in a very cyanotic patient it is possible.

**VAN SLYKE METHOD IN CLINICAL CASES.** A series of clinical cases chosen more or less at random have been studied by the Van Slyke method, using the paraffin oil method for obtaining the plasma. The results are shown in Table III. Throughout this study all figures are the volumes of  $\text{CO}_2$  per cent. reduced to  $0^\circ \text{C}.$ , 760 mm. and corrected for vapor tension. It has seemed to us that the normal limits by this method may be considered as lying between 65 and 80 volumes per cent. Between 55 and 65 volumes per cent. the patients have been, as a rule, mildly nephritic, mildly diabetic, or markedly arteriosclerotic, and might, therefore, be expected to exhibit the slightest grade of acidosis. Below 55 the patients have been for the most part advanced nephritics, except for one moderately severe diabetic and one quite septic case.

**COMPARISON OF THREE METHODS.** In a series of cases we have compared the carbon dioxid capacity of the plasma obtained under paraffin oil, the alveolar air, using the Plesch-Higgins method<sup>10</sup> and the hydrogen ion concentration of the serum by the dialysis method of Levy, Rowntree, and Marriott after blowing off the free  $\text{CO}_2$  from the dialysate as recently suggested by Marriott. The results are shown in Table IV. In general the results agree, but the method of Van Slyke is distinctly the most sensitive of the three and gives much more perfect duplicates than does the method of alveolar air.

**VAN SLYKE METHOD FOLLOWING ANESTHESIA.** The Van Slyke method has been applied to the study of a few cases following nitrous oxide-ether anesthesia. The results are shown in Table V. It will be seen that after from thirty to one hundred and fifteen minutes, ether anesthesia, a lowering of the  $\text{CO}_2$  capacity of the plasma, was constantly observed. The degree to which it was lowered was, in general, proportional to the duration of the anesthesia. In a thirty minutes' anesthesia the lowering was only two to four volumes per cent. while in an anesthesia of one hundred and five minutes it was reduced to forty-nine volumes per cent., about fifteen below the normal. The reduction is apparently at or near its maximum at the close of the anesthesia and exhibits no marked changes in either direction for the next four or five hours, perhaps for, twenty-four hours. The time required for return to normal has not been determined.

In eight of ten cases in which the urine was studied, acetone was studied by the sodium nitroprusside test in the first or second twenty-four hours after operation. The ferric chloride test was positive once. Even when the acetone test was strongly positive, however, the total ketone bodies were never present in more than

TABLE III.—CLINICAL CASES. CO<sub>2</sub> CONTENT OF PLASMA (BLOOD TAKEN UNDER PARAFFIN OIL).

| No.                  | Diagnosis.                     | Age.     | Date.   | Plasma CO <sub>2</sub> . | Alveolar CO <sub>2</sub> . | Blood-pressure. | Blood urea, nitrogen. | Ketonuria gms. per 24 hours. |
|----------------------|--------------------------------|----------|---------|--------------------------|----------------------------|-----------------|-----------------------|------------------------------|
| Controls:            |                                |          |         |                          |                            |                 |                       |                              |
| 1                    | Headache                       | .....    | .....   | 78                       | .....                      | .....           | .....                 | .....                        |
| 2                    | Carcinoma of lip               | .....    | .....   | 78                       | .....                      | .....           | .....                 | .....                        |
| 3                    | Sprain                         | .....    | .....   | 71                       | .....                      | .....           | .....                 | .....                        |
| 4                    | Angioneurotic edema            | .....    | .....   | 71                       | .....                      | .....           | .....                 | .....                        |
| 5                    | Sarcoma of leg                 | .....    | .....   | 71                       | .....                      | .....           | .....                 | .....                        |
| 6                    | Papilloma of bladder           | .....    | .....   | 70                       | .....                      | .....           | .....                 | .....                        |
| 7                    | Pneumonia                      | .....    | .....   | 69                       | .....                      | .....           | .....                 | .....                        |
| 8                    | Varicocele                     | .....    | .....   | 65                       | .....                      | .....           | .....                 | .....                        |
| 9                    | Hemorrhoids                    | .....    | .....   | 65                       | .....                      | .....           | .....                 | .....                        |
| 10                   | Fracture of arm                | .....    | .....   | 65                       | .....                      | .....           | .....                 | .....                        |
| 11                   | Myoma uteri                    | .....    | .....   | 65                       | .....                      | .....           | .....                 | .....                        |
| 12                   | Gastric neurosis               | .....    | Feb. 22 | 70                       | .....                      | .....           | .....                 | .....                        |
|                      | Gastric neurosis               | .....    | Feb. 26 | 64                       | .....                      | .....           | .....                 | .....                        |
|                      | Gastric neurosis               | .....    | Feb. 28 | 66                       | .....                      | .....           | .....                 | .....                        |
| 13                   | Endothelioma                   | .....    | Feb. 5  | 63                       | .....                      | .....           | .....                 | .....                        |
|                      | Endothelioma                   | .....    | Feb. 8  | 65                       | .....                      | .....           | .....                 | .....                        |
| Arteriosclerotics:   |                                |          |         |                          |                            |                 |                       |                              |
| 14                   | Arteriosclerosis               | 57 years | .....   | 68                       | .....                      | 142-85          | 14                    | .....                        |
| 15                   | Arteriosclerosis               | 60 years | .....   | 66                       | .....                      | 150-85          | .....                 | .....                        |
| 16                   | Arteriosclerosis               | 49 years | .....   | 66                       | .....                      | .....           | .....                 | .....                        |
| 17                   | Arteriosclerosis               | 59 years | Feb. 27 | 65                       | .....                      | 170-120         | 17                    | .....                        |
|                      | .....                          | .....    | Mar. 9  | 71                       | .....                      | 170-120         | 29                    | .....                        |
| 18                   | Arteriosclerosis               | 63 years | Mar. 16 | 61                       | .....                      | 230-130         | .....                 | .....                        |
|                      | .....                          | .....    | Mar. 29 | 63                       | .....                      | 230-130         | .....                 | .....                        |
| 19                   | Arteriosclerosis               | 56 years | .....   | 62                       | .....                      | 220-135         | 14                    | .....                        |
| 20                   | Cerebral hemorrhage            | .....    | .....   | 60                       | .....                      | .....           | .....                 | .....                        |
| 21                   | Atrophic oirrhosis             | 56 years | .....   | 57                       | .....                      | 160-120         | 13                    | .....                        |
| Nephritis:           |                                |          |         |                          |                            |                 |                       |                              |
| 22                   | Early nephritis                | 36 years | .....   | 72                       | .....                      | 176-110         | 17                    | .....                        |
| 23                   | Chronic nephritis              | 42 years | .....   | 64                       | .....                      | .....           | 33                    | .....                        |
| 24                   | Early nephritis                | 24 years | .....   | 62                       | .....                      | 198-150         | 14                    | .....                        |
| 25                   | Parenchymatous nephritis       | 21 years | Apr. 17 | 61                       | .....                      | 150-110         | 17                    | .....                        |
|                      | .....                          | .....    | Apr. 19 | 63                       | .....                      | 150-110         | .....                 | .....                        |
|                      | .....                          | .....    | May 6   | 64                       | .....                      | 150-110         | 16                    | .....                        |
|                      | .....                          | .....    | May 15  | 69                       | 48                         | 135-90          | .....                 | .....                        |
| 26                   | Chronic nephritis              | 15 years | .....   | 59                       | .....                      | 165-115         | 23                    | .....                        |
| 27                   | Chronic nephritis              | 45 years | .....   | 59                       | .....                      | 185-135         | 18                    | .....                        |
| 28                   | Acute nephritis                | 30 years | Apr. 12 | 53                       | 30                         | 115-65          | 35                    | .....                        |
|                      | .....                          | .....    | Apr. 27 | 77                       | 55                         | 115-65          | 13                    | .....                        |
| 29                   | Chronic nephritis              | 26 years | .....   | 53                       | .....                      | 140-100         | 21                    | .....                        |
| 30                   | Advanced nephritis             | 44 years | Feb. 25 | 51                       | .....                      | 180-140         | 67                    | .....                        |
|                      | .....                          | .....    | Mar. 4  | 46                       | .....                      | 180-140         | 49                    | .....                        |
|                      | .....                          | .....    | Mar. 8  | 46                       | .....                      | 180-140         | 51                    | .....                        |
| 31                   | Advanced nephritis             | 39 years | Apr. 17 | 48                       | .....                      | .....           | .....                 | .....                        |
|                      | .....                          | .....    | Apr. 27 | 55                       | .....                      | .....           | 116                   | .....                        |
|                      | .....                          | .....    | May 6   | 48                       | .....                      | .....           | 119                   | .....                        |
|                      | .....                          | .....    | May 12  | 46                       | 35                         | .....           | 142                   | .....                        |
| 32                   | Advanced nephritis             | 55 years | .....   | 37                       | 33                         | 190-100         | 142                   | .....                        |
| 33                   | Advanced nephritis             | 56 years | .....   | 35                       | 25                         | 158-80          | 122                   | .....                        |
| 34                   | Advanced nephritis             | 34 years | Mar. 27 | 40                       | .....                      | 178-115         | 195                   | .....                        |
|                      | .....                          | .....    | Mar. 29 | 33                       | .....                      | 178-115         | .....                 | .....                        |
| Mercurial nephritis: |                                |          |         |                          |                            |                 |                       |                              |
| 35                   | Biochloride poisoning (severe) | 21 years | June 6  | 70                       | .....                      | 120-75          | 16                    | .....                        |
|                      | .....                          | .....    | June 7  | 70                       | .....                      | 120-75          | 20                    | .....                        |
|                      | .....                          | .....    | June 15 | 71                       | .....                      | 120-60          | 17                    | .....                        |
| 36                   | Biochloride poisoning (mild)   | 24 years | June 12 | 70                       | .....                      | 115-70          | 14                    | .....                        |
|                      | .....                          | .....    | June 15 | 70                       | .....                      | 120-75          | 13                    | .....                        |
| Eclampsia:           |                                |          |         |                          |                            |                 |                       |                              |
| 37                   | Eclampsia                      | .....    | .....   | 57                       | .....                      | .....           | 21                    | .....                        |
| 38                   | Eclampsia                      | .....    | .....   | 52                       | .....                      | .....           | 29                    | .....                        |
| 39                   | Eclampsia                      | .....    | .....   | 52                       | 35                         | .....           | 20                    | .....                        |
| 40                   | Eclampsia                      | .....    | .....   | 48                       | .....                      | .....           | 13                    | .....                        |
| 41                   | Eclampsia                      | .....    | Mar. 28 | 46                       | .....                      | .....           | .....                 | .....                        |
|                      | .....                          | .....    | Mar. 30 | 57                       | .....                      | .....           | 14                    | .....                        |
| Septic:              |                                |          |         |                          |                            |                 |                       |                              |
| 42                   | Pelvic inflammation            | 32 years | Feb. 29 | 52                       | .....                      | 195-120         | 12                    | .....                        |
|                      | .....                          | .....    | Mar. 27 | 63                       | .....                      | .....           | .....                 | .....                        |
| Diabetes:            |                                |          |         |                          |                            |                 |                       |                              |
| 43                   | Mild                           | 48 years | .....   | 71                       | .....                      | .....           | .....                 | 2.0                          |
| 44                   | Mild                           | 25 years | .....   | 64                       | .....                      | .....           | .....                 | 0.4                          |
| 45                   | Mild                           | 51 years | .....   | 60                       | .....                      | .....           | .....                 | 2.0                          |
| 46                   | Mild                           | 35 years | Mar. 8  | 52                       | .....                      | .....           | .....                 | 4.6                          |
|                      | .....                          | .....    | Mar. 29 | 64                       | .....                      | .....           | .....                 | 0.4                          |

The blood urea nitrogen estimations in the table were performed by the urease method (Van Slyke and Cullen); the urinary ketones by Schaffer's method.

very small amounts, the largest amount excreted in twenty-four hours being 0.83 mgm. expressed as acetone (Shaffer's method). The total acid output by Henderson's and Palmer's method was normal.

TABLE IV.—COMPARISON OF CO<sub>2</sub> CONTENT OF PLASMA, CO<sub>2</sub> TENSION OF ALVEOLAR AIR AND HYDROGEN ION CONCENTRATION OF SERUM AFTER AERATION OF DIALYSATE.

| Case No. | CO <sub>2</sub> content plasma. | CO <sub>2</sub> tension alveolar. | Hydrogen ion of serum. |
|----------|---------------------------------|-----------------------------------|------------------------|
| 1        | 77                              | 44                                | 8.1                    |
| 2        | 72                              | 50                                | 8.0                    |
| 3        | 69                              | 48                                | 8.0                    |
| 4        | 67                              | 43                                | 8.0-                   |
| 5        | 65                              | 50                                | 7.9                    |
| 6        | 64                              | 39                                | 8.0                    |
| 7        | 63                              | 41                                | 8.0                    |
| 8        | 62                              | 38                                | 8.1                    |
| 9        | 58                              | 44                                | 8.1                    |
| 10       | 52                              | 40                                | 8.0                    |
| 11       | 52                              | 35                                | 7.9                    |
| 12       | 46                              | 35                                | 7.9                    |
| 13       | 37                              | 33                                | 7.7                    |

TABLE V.—EFFECT OF ETHER ANESTHESIA ON CO<sub>2</sub> CONTENT OF PLASMA.

| Case No. | Operation.           | Age. | Duration of anesthesia, minutes. | CO <sub>2</sub> content: |                  |
|----------|----------------------|------|----------------------------------|--------------------------|------------------|
|          |                      |      |                                  | Before.                  | After.           |
| 1        | Carcinoma of lip     | 72   | 30                               | 73                       | 69               |
| 2        | Amputation of leg    | 17   | 30                               | 70                       | 66               |
| 3        | Amputation of leg    | 30   | 30                               | 65                       | 63               |
| 4        | Herniorrhaphy        | 20   | 35                               | ..                       | 64               |
| 5        | Hemorrhoids          | 19   | 35                               | 65                       | 59               |
| 6        | Perineal, plastic    | 51   | 40                               | ..                       | 56               |
| 7        | Nephrotomy           | 30   | 50                               | ..                       | 60               |
| 8        | Ectopic pregnancy    | 35   | 50                               | ..                       | 53 <sup>10</sup> |
| 9        | Nephrotomy           | 48   | 70                               | ..                       | 59               |
| 10       | Perineal, plastic    | 46   | 85                               | ..                       | 47 <sup>10</sup> |
| 11       | Suprapubic cystotomy | 24   | 90                               | 70                       | 60               |
| 12       | Pan hysterectomy     | 56   | 100                              | ..                       | 53 <sup>10</sup> |
| 13       | Pan hysterectomy     | 58   | 105                              | ..                       | 51               |
| 14       | Pan hysterectomy     | 19   | 105                              | ..                       | 49 <sup>10</sup> |
| 15       | Pan hysterectomy     | 35   | 110                              | 65                       | 57               |
| 16       | Gastrojejunostomy    | 39   | 115                              | ..                       | 56               |

Four of the patients received just at the close of the anesthesia two pints each of 5 per cent. glucose solution per rectum. These cases showed quite as marked a reduction of the carbonate content of the plasma as did comparable cases not receiving the glucose.

The cause of acidosis is different in different conditions. In diabetes it is due largely to the presence in the blood of the ketone acids. In nephritis and severe diarrhea it is probably, according to Howland and Marriott,<sup>11</sup> due to an impaired capacity on the

<sup>10</sup> Received glucose per rectum at close of anesthesia.

<sup>11</sup> Acidosis Occurring with Diarrhea, *Am. Jour. Dis. of Child.*, 1916, xi, 309.

part of the kidneys to excrete phosphoric acid. For other types the cause of the acidosis is not known. That the clinical symptomatology varies somewhat with the type and cause of the acidosis is apparently true. Whether the treatment of acidosis, *per se*, apart from its cause will be of importance remains to be determined. Henderson has urged that in any conditions associated with reduction in the buffer value of the blood, sodium bicarbonate be given by mouth to the point of rendering the urine less acid, but not distinctly alkaline. Using this simple criterion one may endeavor to replenish the supply of buffer substances in the blood and yet avoid overtaxing the system with excessive alkali. In this connection attention may be called to the suggestion of Magnus-Levy<sup>12</sup> that in giving sodium carbonate solutions intravenously for the treatment of severe acidosis the injection of a highly alkaline solution may well be a severe insult to the system. He suggested that a safer plan is to pass CO<sub>2</sub> gas through the sterile sodium carbonate solution, to which a drop of phenolphthalein has been added, until the solution is colorless, when it becomes more closely analogous to the normal sodium carbonate-carbon dioxid buffer of the blood—the reaction of which is nearly neutral—the substance which one is aiming by such injections to replace.

CONCLUSIONS. 1. In the new methods for studying acidosis directly from the blood we have a means of investigation that constitutes a distinct advance upon our previous methods.

2. As criteria of the supply of "buffer substance" in the blood the carbon dioxid capacity of the plasma (Van Slyke, Stillman, and Cullen method) the hydrogen ion concentration of the serum (Levy, Rowntree, and Marriott method) and the alveolar air (Plesch-Higgins method) give results that are in general parallel. The first of these is the most sensitive of the three and gives much more satisfactory duplicates than does the alveolar air determination. It affords a simple and quick method of determining the presence and degree of acidosis.

3. In using the method for the CO<sub>2</sub> capacity of the plasma, and presumably in any method intended to measure directly or indirectly the alkalinity of the plasma, the CO<sub>2</sub> concentration of the whole blood must be kept unchanged or brought to a standard tension while centrifuging and separating the plasma from the cells.

4. Asphyxia or any condition of high CO<sub>2</sub> tension in the blood *in vivo* raises the CO<sub>2</sub> capacity of the plasma if the latter is separated by the paraffin oil method, and may interfere with the recognition of a slight acidosis. This may be overcome by saturating the whole blood at a standard CO<sub>2</sub> tension before centrifuging and maintaining this tension until the plasma is pipetted off.

<sup>12</sup> Ueber subkutane Infusionen von Mononatriumkarbonat, Therap. Monatsch., 1913, xxvii, 838.

5. By the Van Slyke method the normal CO<sub>2</sub> capacity of the plasma reduced to 0° 760 mm. pressure and correcting for vapor tension appears to be about sixty-five to eighty volumes per cent. This is slightly reduced in arteriosclerotic conditions and moderately to markedly reduced in diabetes and nephritis, especially in the advanced stage.

6. After ether anesthesia there is a depression of the CO<sub>2</sub> capacity of the plasma of from two to twenty volumes per cent. This depression is proportional to the duration of the anesthesia. The lowest figure observed was 47. This reduction is present and probably maximal at the close of the anesthesia, and apparently remains little altered for at least five hours. A single injection of two pints of a 5 per cent. glucose solution per rectum at the close of the anesthesia does not lessen the reduction in the CO<sub>2</sub> capacity during the next five hours.

---

## THE TOXEMIAS OF PREGNANCY.

BY J. R. LOSEE, M.D.,

AND

DONALD D. VAN SLYKE, PH.D.,

NEW YORK.

(From the Lying-in Hospital and the Hospital of the Rockefeller Institute for Medical Research, New York.)

ALTHOUGH no general agreement has been reached concerning the nature of the substances causing the toxemias of pregnancy, two explanations have claimed special consideration. Ewing and Wolf,<sup>1</sup> noting the anatomical changes of the liver in eclampsia, the facts that leucine and tyrosine had been reported in eclamptic urines, and that they themselves found often a decrease in urea and an increase in the "undetermined nitrogen" fraction of the urine, suggested that the amino-acids were incompletely catabolized in the degenerated liver, and were the cause of both the toxemia and the abnormal nitrogen distribution. Later Murlin and Bailey,<sup>2</sup> also working in the Cornell laboratory, attacked the same problem with the aid of Soerensen's formol titration method, which is specific for amines and amino-acids. They decided that not only the amino-acid fraction, but also the other nitrogen fractions of the urine are likely to be within the limits of normal variation both before and immediately after the convulsions of eclampsia, and that consequently the nitrogen distribution in the urine offers no reliable

<sup>1</sup> Am. Jour. Obst., 1906, lv, 289.

<sup>2</sup> Jour. Am. Med. Assn., 1912, lxx, 1522.